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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,925	09/24/2003	William Hildebrand	66802.055	4622

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,925	HILDEBRAND ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-42,45,46,48-51,60 and 61* is/are pending in the application.

4a) Of the above claim(s) *38-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-37, 42, 45, 46, 48-51, 60, 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed 11/16/09 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I and species of ELISA plate as the substrate, antibody as the anchoring moiety, W6/32 as the antibody, as well as Applicant's election of the species of HLA-A2 with traverse in Applicant's amendment and response filed 12/1/06.

Claims 31-37, 42, 45, 46, 48-51, 60 and 61 are currently being examined.

3. Applicant's amendment filed 11/16/09 has overcome the prior rejection of record of claims 31-37, 42, 45-51, 60 and 61 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter rejection at item #4 in prior Office Action of record).

4. Applicant's amendment filed 11/16/09 has overcome the prior rejection of record of claims 31-37, 42, 45, 46, 48-51, 60 and 61 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter rejection at item #5 in prior Office Action of record).

5. Applicant is reminded that for the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the instant application, *i.e.,* 9/24/03, as the parent applications do not support the claimed limitations of the instant application. The provisional parent application serial no. 60/413,842 only discloses ELISA assays using W6/32 or pan-HLA antibody immobilized HLA to detect anti-HLA antibodies. The provisional parent application serial no. 60/474,655 discloses some aspects of making soluble HLA from gDNA or cDNA. The parent application serial no. 10/337,161 and 10/022,066 disclose soluble HLA and making soluble HLA, respectively. In addition, the provisional parent applications do not disclose "pool" in the context of the claimed method.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 31-37, 45, 46, 49-51, 60 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

This is a new ground of rejection necessitated by Applicant's amendment filed 11/16/09.

Claim 31 recites "linking a soluble MHC trimolecular complex to a substrate, wherein the soluble MHC trimolecular complex…". However, the "purifying" step recited prior to the "linking" step recites "purifying the individual, soluble MHC trimolecular complexes", plural. The current claim language recites that ***only one*** soluble MHC trimolecular complex out of the plurality of complexes, rather than the plurality of complexes, are linked to the substrate.

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8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 31-37, 42, 45, 46, 48-51, 60 and 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,482, 841 (IDS reference) in view of U.S. Patent No. 5,292,641 (IDS reference), U.S. Patent No. 6,232,445 (IDS reference), DiBrino *et al* (Biochemistry. 1995, 34(32): 10130-10138, of record) and Zemmour *et al* (J. Immunol. 1992, 148(6): 1941-1948, of record) and by an admission in the specification at page 42 and Figure 7.

U.S. Patent No. 5,482, 841 discloses an assay method for detecting the presence of anti-HLA antibodies in a sample, said assay comprising HLA molecules extracted from cells and purified by detergent extraction, centrifugation, PEG and NH_4SO_4 precipitation, said HLA molecules indirectly linked to a solid support such as beads, membranes and microtiter plates by polyclonal or monoclonal antibodies specific for the α3 domain of Class I HLA or the associated β2m chain or to a conformational epitope expressed by the combination of both chains, or specific to epitopes conserved across a class or subset of HLA molecules, such as ones specific for HLA-A, B or C. U.S. Patent No. 5,482, 841 further discloses that a sample containing antibodies is added, bound antibodies are separated from free antibodies and other non-specifically bound proteins or other components, and the presence of the antibodies is detected using a labeled reagent such as anti-human antibody against IgG, IgM or IgA. U.S. Patent No. 5,482, 841 discloses that the samples may be biological fluids such as blood, CSF, tears, saliva, lymph, dialysis fluid, organ or tissue culture derived fluids and fluids extracted from physiological tissues. U.S. Patent No. 5,482, 841 discloses that of particular interest are allo-antibodies found in the serum of transplant or prospective transplant patients, and that the determination of the presence and specificity of antibodies against foreign HLA antigens is therefore clinically important for monitoring transplant patients, and the assay may test for reactivity against a panel of antigens or may be specific for a single donor. U.S. Patent No. 5,482, 841 discloses that the solid support can be microtiter plates (with wells), glass, plastic, polysaccharides, nylon or nitrocellulose [membranes] or paramagnetic component materials surrounded by plastic. U.S. Patent No. 5,482, 841 discloses using negative and positive control samples. U.S. Patent No.

5,482, 841 discloses a kit for use in a method for detecting at least one receptor analyte specific for an HLA antigen in a biological sample, said kit comprising a solid support coated with a capture agent capable of specifically binding to a conserved region of a subset of interest of HLA antigens and a labeled reagent that specifically binds to human antibodies, and wherein the capture agent may be an antibody directed to the $\alpha 3$ domain of HLA class I heavy chain (see entire reference).

U.S. Patent No. 5,482, 841 does not disclose wherein the pool of HLA molecules is recombinantly produced as recited in the instant claims.

U.S. Patent No. 5,292,641 discloses a kit that includes HLA antigens bound to a solid support, control solutions, and the reagents necessary for the determination of antibodies specific for the HLA antigens (especially column 5 at lines 35-49). U.S. Patent No. 5,292,641 discloses an assay method that utilizes HLA bound to a solid support, said HLA being Class I or Class II or minor histocompatibility antigens and derived from human donors, including from platelets, plasma, serum, lymphoblastoid cell lines, transfectant cell lines, or any other convenient source, said solid support including microtiter plate wells, test tubes, beads, slides, absorbent films, membranes, particles, magnetic particles, glass or plastics. U.S. Patent No. 5,292,641 discloses ELISA techniques and the use of labeled anti-human bodies for detection (see entire reference).

U.S. Patent No. 6,232,445 discloses large-scale production of large quantities of an individual, functional, soluble MHC molecule, including an MHC class I HLA molecule. US 6,232,445 discloses isolation of total mRNA from total mRNA from an immortalized cell line source, reverse transcribing mRNA to form cDNA, PCR amplification of MHC molecules truncated to exclude the transmembrane and cytoplasmic domains (*i.e.,* including a stop codon and thus making it soluble), cloning the PCR product into a mammalian expression vector comprising a promoter, and that the soluble MHC molecule may comprise a tail or tag such as 6x-His that can be used for purification, or alternatively, an anti-HLA antibody specific for a conformational epitope may be used for immunoaffinity purification of properly folded HLA molecules, including an elution from the anti-HLA antibody at pH 11 that leaves the complex intact. US 6,232,445 discloses transfection the mammalian expression vector into a variety of cell types including the mammalian cell line HeLa that is a human ovarian cancer cell line (that has endogenous peptides that can load into the antigen binding groove of the HLA class I molecule) and inoculating hollow fiber bioreactors for large scale continuous production of soluble individual and functional individual MHC class I molecules. While the examples recited in U.S. Patent No. 6,232,445 used MHC class II molecules for exemplification of the method, U.S. Patent No. 6,232,445 discloses that both MHC class II and class I molecules are embraced by the practice of the method. Furthermore, it is well within the purview of the artisan to obtain primers for practicing the method of U.S. Patent No. 6,232,445 and use them to amplify the extracellular domains of MHC class I in the same manner as the MHC class II molecules exemplified (see entire reference, especially

column 25 at lines 42-65, column 27 at lines 7-26, column 28 at lines 49-67, column 29 at lines 34-67, column 31 at lines 48-54, column 47 at lines 31-54, claim 7, column 48 at lines 55-67, column 49 at lines 1-3, column 54 at lines 45-67, column 58 at lines 1-14, column 2 at lines 50-67, column 3 at lines 1-47, figure 5B).

DiBrino *et al* teach obtaining and full length cDNA for HLA-B*4403 by PCR amplification of cDNA made from RNA isolated from the immortalized human lymphoblastoid B cell line W1B. The cDNA was sequenced, cloned into the expression vector RSV.neo and transfected into Hmy2.C1R cells (class I deficient cell line). DiBrino *et al* teach detection of said HLA using W6/32 monoclonal antibody specific for human Class I molecules. DiBrino *et al* teach HLA-A2 class I HLA molecules. DiBrino *et al* teach a truncated HLA class I molecule lacking the transmembrane and cytoplasmic regions (especially materials and methods section).

Zemmour *et al* teach that Hmy2.C1R cells express HLA-Cw4 as well as reduced levels of HLA-B35 (especially abstract).

The admission in the specification at page 42 and Figure 7 is that soluble HLA retains its structure and bound peptide when eluted with pH 11.0 buffer.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have provided soluble, recombinantly produced HLA molecules and to have used them in the method for determining anti-HLA antibodies disclosed by U.S. Patent No. 5,482, 841 and U.S. Patent No. 5,292,641.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to disclosed by U.S. Patent No. 6,232,445 or the Hmy2.C1R cell line taught by DiBrino *et al* and by Zemmour *et al*, and including the use of W6/32 antibody as a capture agent, and to have included a step of obtaining cDNA encoding class I by reverse transcribing RNA isolated from an immortalized human cell line as taught by DiBrino *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide a more easily produced and easily purified source of soluble HLA molecules for use in the method for detecting the presence of anti-HLA antibodies in a sample.

With regard to the limitation "wherein the mammalian cell line expresses endogenous MHC molecules" recited in base claim 31, two references cited in the instant rejection teach the cell line Hmy2.C1R that does express endogenous MHC molecules, and thus the art meets the said claim limitation.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 11/16/09 on pages 9-14.

With regard to Applicant's arguments about making a soluble single chain HLA class I construct, the following applies.

Applicant argues that the soluble class I MHC trimolecular complexes produced in the presently claimed method are naturally assembled within the cell to form heterotrimers comprising the recombinantly introduced heavy chain, naturally or endogenously produced light chain (β2m) and endogenously loaded antigenic peptides, whereas previous technologies such as disclosed in '445 cited in the instant rejection have relied on strategies to artificially link the heavy chain and β2m plus or minus the peptide. However, the claim language (in base claim 31) does not preclude that the HLA class I molecule can not be a single chain molecule. The step of culturing recites "such conditions also allowing for endogenous loading of a peptide ligand into the antigen binding groove…in the presence of β2-microglubulin", and β2-microglubulin is present in a single chain molecule. The obtaining steps do not preclude construction of a single chain MHC class I molecule, and the transitional language of the said base claim is "comprising." Thus, the claims do not recite that the heavy chain must associate with heterologous (*i.e.,* cell derived) β2m, just that the conditions allow for endogenous loading of a peptide ligand in the presence of β2m prior to secretion of the trimolecular complex. Furthermore, "trimolecular complexes" recited in the instant claims is not defined in the instant specification. Hence, the instant claims are not limited to method steps that produce a heavy chain that is not fused to β2m.

Also, in presenting arguments directed to chaperones and trafficking of class I heavy chains, Applicant is arguing limitations that are not recited in the instant claims. The instant claims do not recite that the soluble MHC complexes bind only the strongest binding peptides that remain associated when β2m exchange occurs.
In addition, Applicant does not present evidence, but rather alleges that the single chain HLA class I molecules will not load the same peptide pool as non-single chain HLA class I molecules.

With regard to Applicant's argument about superiority of truncated MHC *versus* detergent solubilized MHC, the instant rejection does not propose to detergent-solubilize the HLA class I molecules. It proposes to truncate the nucleic acid molecule encoding the HLA class I heavy chain to exclude the transmembrane and cytoplasmic regions and thus produce a soluble molecule that can be purified away from the other HLA class I molecules. Thus, Applicant's further arguments as to the disadvantage of detergent solubilization taught by DiBrino *et al* are moot. In addition, DiBrino *et al* as well as the '841 and '641 patents are being argued separately.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.1986).

Furthermore, with regard to Applicant's arguments directed at DiBrino *et al*, it would have been prima facie obvious to have used the art known methods to produce a soluble version of the construct taught by DiBrino *et al*. One of ordinary skill in the art at the time the invention was made would have been motivated to do this for simplicity sake, particularly in light of the teaching of DiBrino *et al* that HLA class I heavy chain that is truncated to remove the transmembrane and cytoplasmic regions will associate with β2m and peptide *in vitro*, and that DNA encoding HLA class I heavy chain, when transfected into a cell, will associate with the cell's endogenous β2m and acquire an endogenous peptide.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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